

Tropical diseases and the poor

Neglected tropical diseases are a public health problem for developing and developed countries alike

Philip Hunter

For decades, public health experts and economists have been warning of the enormous human toll and economic losses exerted by tropical diseases, notably malaria, dengue fever, and sleeping sickness. Funding agencies, philanthropies, and pharmaceutical companies have invested millions of dollars and euros into research to find a cure or vaccine. But while these major killers have drawn most of the public, funders' and scientists' attention, it has become clear during the past few years that many other "neglected tropical diseases" (NTDs) also have a considerable impact on the populations and economies of developing countries (Fig 1).

More recently still, NTDs have become a growing problem for the affluent nations of Europe, North America, South-East Asia, and Australasia where they predominantly affect the poor and disenfranchised. Peter Horte, from the National School of Tropical Medicine at Baylor College of Medicine, Houston, Texas, USA, therefore coined the term "blue marble health"—in reference to an iconic photograph of Earth taken from space—to underline that NTDs occur everywhere on the planet and affect the poor in every country. "I have given this name to differentiate them from old global health paradigms [diseases such as malaria and TB with higher levels of fatality]," said Horte, who specializes in NTDs in developed countries, especially the USA.

Although there are many differences between the NTDs and how they affect their victims, the disease profiles are similar in terms of their adverse impact on child development, pregnancy outcome, and worker productivity [1]. In both developed and developing nations, NTDs tend to have low mortality, measured in years lost,

but high morbidity, measured in years lived with some form of disability [2]. This translates into high measures of DALYs (disability-adjusted life years) lost, which is a common measure of how disease impacts on quality of life and equates to economic productivity.

There are two other important characteristics of NTDs common among many nations. At least in the USA and the developing nations of Latin American and the Caribbean region, these diseases disproportionately affect indigenous and colored people, after taking wealth into account [3]. The situation is similar in parts of Europe where some immigrant groups and Romani people tend to suffer more than others of comparable economic status, according to Horte. The second common aspect of NTDs is that treatment is relatively inexpensive. They average cost is US\$ 0.50 per person per year, compared with US\$ 6.64 for malaria and US\$ 700 for HIV/AIDS, according to the Social and Economic Impact Review on Neglected Tropical Diseases by the Hudson Institute's Centre for Science in Public Policy in conjunction with The Global Network for Neglected Tropical Diseases (<http://www.end.org/downloads/20121101%20Hudson%20Institute%20and%20Sabin%20Institute%20-%20Social%20and%20Economic%20Impact%20Review%20on%20Neglected%20Tropical%20Diseases.pdf>). This factor, combined with a growing appreciation of NTDs' impact "below the radar" on health surveillance programs, culminated in 2003 in the Drugs for Neglected Diseases Initiative (DNDi), based in Geneva, Switzerland. It is a non-profit drug development organization that aims to deliver new treatments for 11 NTDs by 2018; so far, it has concentrated its efforts on leishmaniasis, Chagas disease, and human African trypanosomiasis. Although the DNDi focuses mostly

on NTDs in the developing world, it essentially takes a global view, according to its executive director Bernard Pécoul. "We are well informed about and monitoring what is going in developing countries," said Pécoul.

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The World Health Organization (WHO) has identified 17 NTDs as important research targets (http://www.who.int/neglected_diseases/diseases/en/). These are for instance rabies, which is present almost everywhere in the world, as well as several river and foodborne diseases, which are almost entirely confined to the tropics (Table 1). The list includes also various diseases that had been considered predominantly tropical but have recently become a problem in developed countries; Pécoul singled out two in particular: Chagas disease and leishmaniasis. Both are caused by protozoan parasites, but have different symptoms and pathologies that reflect their impact and distribution.

Leishmaniasis is caused by protozoa of the genus *Leishmania*; the vectors are various species of the sand fly. It is largely a zoonotic disease and depends on a suitable population of animals as a repository for the parasite, according to Pécoul. As a result, the distribution of leishmaniasis

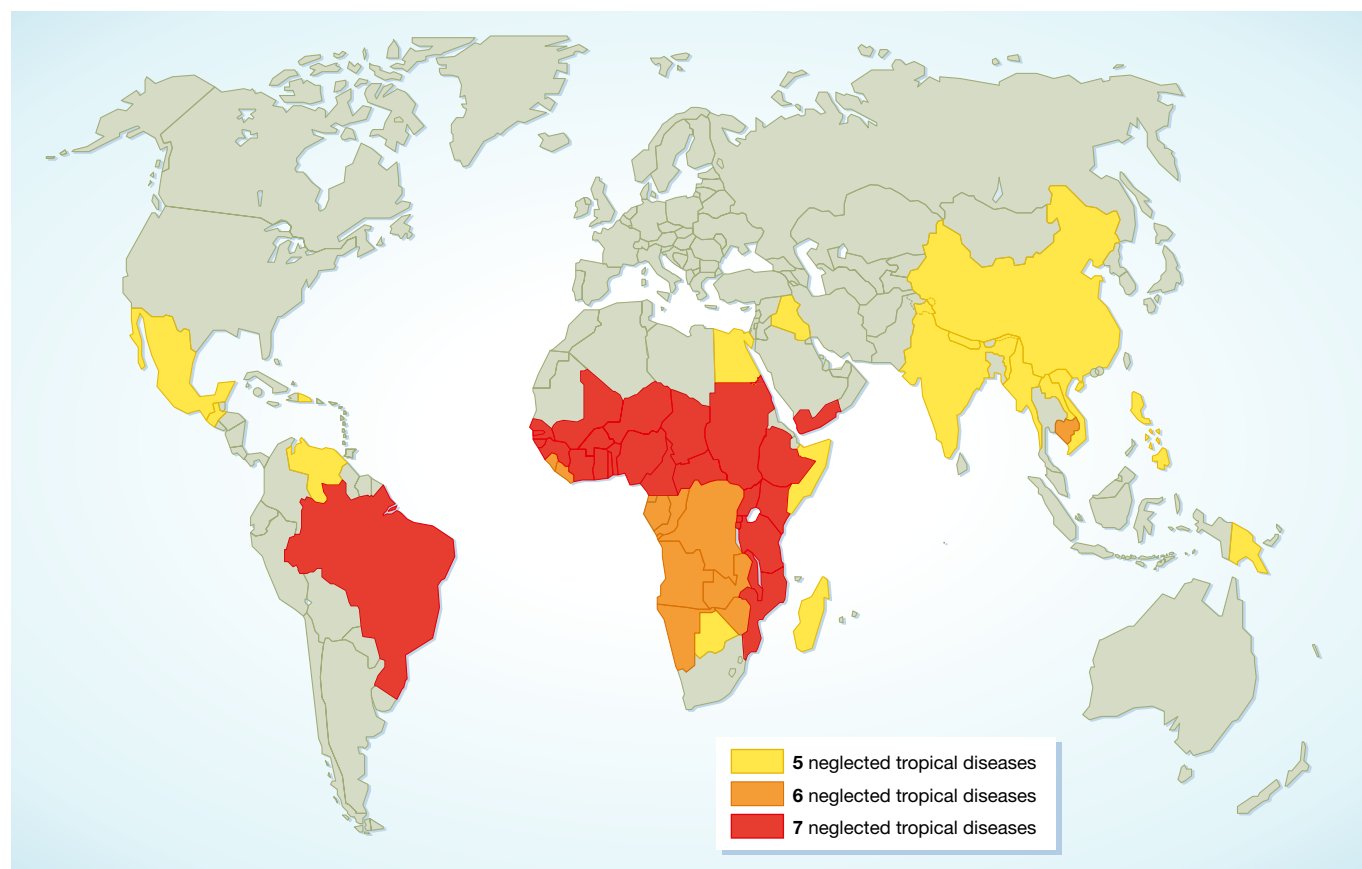


Figure 1. Global distribution of neglected tropical diseases. Adapted from Hotez *et al* (2009).

in developed countries varies a lot and has only low levels in many regions. Yet, Pécoul highlighted an ongoing European outbreak in the area around Madrid as a cause of concern. This outbreak was first identified in July 2009 in the southwest of the Spanish capital and affected residents from four villages that share extensive park areas—this is an important factor because dogs are susceptible to the disease through sand fly bites. “In that Madrid case, everything is present to facilitate transmission of leishmaniasis,” explained Pécoul. “The vector is present and among dogs there is a huge reservoir of parasites in the south of Europe and a lot of transmission to dogs.” As of December 2012, there were 446 reported cases in Spain, representing a mean incidence rate of 22.2 per 100,000 inhabitants since July 2009, making it Europe’s biggest reported community outbreak of leishmaniasis to date. Pécoul warned that even people from Northern Europe were at risk of catching the disease

when visiting Spain, especially if they have their dogs with them.

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Symptoms emerge gradually in the form of skin sores or ulcers weeks or even months after the victim has been bitten. More serious complications can follow a few months to years after infection, including fever, damage to the spleen and liver, and anemia. These are usually associated with a more severe form of the disease called visceral leishmaniasis, which is more likely to afflict vulnerable people with weakened immune systems, notably HIV/AIDS sufferers. “The link with HIV/AIDS was more of an

issue during the 1980s and 1990s because when you treat HIV you decrease the risk of co-infection,” commented Pécoul. Modern antiretroviral drug treatments for HIV/AIDS, readily available in Europe, alleviate the impact on the immune system and reduce the severity of leishmaniasis in the event of co-infection. There is little transmission of leishmaniasis in the USA, but it has been more of an issue for the country’s servicemen stationed abroad. “There has been a lot coming back from Afghanistan or Iraq, places where a lot of transmission occurs,” explained Pécoul.

The USA itself has been more afflicted by Chagas disease, named after the Brazilian physician Carlos Chagas who first described it in 1909. It is caused by the protozoan *Trypanosoma cruzi*, which is commonly transmitted to humans and other mammals by an insect vector, the blood-sucking “kissing bugs” of the subfamily *Triatominae*. It can also be transmitted from

Table 1. The 17 neglected tropical diseases

Buruli ulcer (<i>Mycobacterium ulcerans</i> infection)
Chagas disease
Dengue/severe dengue
Dracunculiasis (guinea-worm disease)
Echinococcosis
Foodborne trematodiasis
Human African trypanosomiasis (sleeping sickness)
Leishmaniasis
Leprosy
Lymphatic filariasis
Onchocerciasis (River blindness)
Rabies
Schistosomiasis
Soil-transmitted helminthiasis
Taeniasis/cysticercosis
Trachoma
Yaws (endemic treponematoses)

mother to child and by blood transfusion from an infected person. Its incidence in the USA and Europe is usually linked to immigration, but also due to the insect vectors in the extreme south of the USA, according to Pécoul.

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“By applying published seroprevalence figures to immigrant populations, CDC (Centers for Disease Control and Prevention) estimates that more than 300,000 persons with *Trypanosoma cruzi* infection live in the United States,” said Monica Parise, the CDC’s head of parasitic infections. Indeed, the incidence of Chagas is now increasing across both the USA and Europe, according to Pécoul. Again, Spain seems to be affected worst, with around 70,000 people infected [4].

The pathology of Chagas has an early acute phase, followed by a chronic condition that is potentially more serious. Symptoms in the acute phase involve local swelling around the site of the bite and antiparasitic drug treatment yields a complete cure in about 60–85% of adults and more than 90%

of infants treated in the first year of acute phase. However, the success of drug treatments in clearing the pathogen diminishes significantly after even four to eight weeks by which time the infection enters a chronic phase in 20–40% of Chagas sufferers who often develop life-threatening cardiac or digestive disorders.

In the case of leishmaniasis, a number of drugs have been tried with varying degrees of success. The most promising candidate is miltefosine, which was initially developed in the late 1980s as an anticancer agent by German scientists Hansjörg Eibl and Clemens Unger. The drug is also effective against the *Leishmania* protozoa and is now being used as a broad-spectrum antimicrobial drug against pathogenic bacteria and fungi: it targets the phospholipids that are major components of the parasites’ cell membranes. Yet, even if drugs are important, it requires sound public health policies in addition to therapeutic measures, according to Parise. She singled out Chagas in particular given that two available drugs, nifurtimox and benznidazole, have serious side effects. The CDC’s efforts to deal with the disease include education of health professionals, supporting physicians and patients with diagnostic testing, developing improved diagnostic tests for Chagas disease and ways to determine whether treatment has been successful, and collaborating with investigators to determine the congenital risk of Chagas disease among at-risk mothers, Parise commented.

While Chagas and leishmaniasis are the leading NTDs in North America and Europe, the situation is different in other developed nations where Buruli ulcer can be an equally significant disease: in 2013, 105 cases were reported in Australia (http://apps.who.int/neglected_diseases/ntddata/buruli/buruli.html). This disease is caused by *Mycobacterium ulcerans*, which is related to *Mycobacterium leprae*, the cause of leprosy and the *Mycobacteria* that cause tuberculosis. As the name indicates, Buruli ulcer is a chronic, debilitating infection characterized by skin ulcerations that expand into necrotizing lesions of dead skin and occasionally surrounding bone, which, if untreated, leads to permanent scarring and in some cases requiring amputation. It is largely confined to tropical and subtropical areas but it also afflicts parts of Australia and other countries including Japan.

Alongside treatment, research has focused particularly on the transmission mechanism, which remains largely unknown; it has gained Buruli ulcer the term “the mysterious disease”. It is associated with tropical and subtropical aquatic environments, and *M. ulcerans* has been detected as biofilms on surfaces, including adult mosquitoes [5]. But it has yet to be established beyond doubt whether it spreads to humans via mosquito bites, or some form of contamination from the environment. Direct human-to-human transmission has not been observed except in one case, but there is evidence that it occurs as a zoonosis, according to John Wallace, a medical entomologist specializing in Buruli ulcer at Millersville University in Pennsylvania, USA. “BU cases have been confirmed in multiple mammalian species, such as Koala, Potoroo, Possums, horses, and dogs and there may be a few others such as roos and maybe a snake too,” he said.

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But even the latest research does not finally resolve the mystery, since it seems to suggest that the bacterium does not cause infection via open wounds. “We have a paper under review based on laboratory work showing that we are unable to get infection in a guinea pig model of infection simply by dropping bacteria on an open wound,” Wallace explained. “The results were totally unexpected in that the bacteria must be injected into the skin to establish infection. This was quite surprising because if you drop Staph or other infectious skin pathogens on an open wound, they do replicate and cause disease. Although it was a lab study, we think it provides fairly good evidence that the bacteria are not likely to establish infection passively through an open wound.” One reason it has proved difficult to establish the transmission mechanism for *M. ulcerans* is the long incubation period, which makes it hard to associate infection with a particular incident such as an insect bite or skin abrasion, according to Wallace.

At least progress has been made over treatment. Until a decade ago, the disease failed to respond to antibiotics and surgery was the only recourse to excise damaged tissue followed by skin grafting. But this is usually impractical and unaffordable on large lesions on patients in rural West Africa where it is endemic. Even in Australia, it resulted in scarring in many cases. Yet, a few years ago, it was found that a combination of rifampin and streptomycin for 8 weeks can kill *M. ulcerans* bacilli, arrest the disease, and promote healing so as to reduce the extent of surgical excision [6].

Meanwhile, there are signs of leprosy returning to some parts of the developed world, especially the USA, according to Masanori Matsuoka from the Leprosy Research Center, National Institute of Infectious Diseases in Tokyo, Japan. Although it is related to *M. ulcerans*, *M. leprae* exhibits a different transmission pattern, via nasal droplets. Unlike Buruli ulcer or Chagas, it is also not endemic but maintained at low levels through immigration. “There is concern of leprosy increasing in the US as many cases are imported from

countries in the Pacific Ocean such as Micronesia and Marshall island,” said Matsuoka. “New case detection rate is extremely high in these countries.” At least, leprosy is readily treatable via multiple antibiotics without the issue over emergence of resistant strains as there are with TB.

The developed world thus cannot just simply ignore NTDs even if they are not affected to the same degree as developing countries and not by all 17 diseases prioritized by the WHO. While their distribution, transmission, and treatment options are very different, all these diseases revolve around poverty and require, beyond treatment, improved surveillance, diagnosis, and education within local communities to contain them.

Conflict of interest

The author declares that he has no conflict of interest.

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